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**Exhibit 9**

ORIGINAL ARTICLE

# Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma

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*Key words:* Asthma – Budesonide – Budesonide/formoterol – Exacerbations – Inhaled corticosteroids – Long-acting $\beta_2$-agonists – Single inhaler

## SUMMARY

*Objectives:* This study evaluated the efficacy and safety of a novel asthma management strategy – budesonide/formoterol for both maintenance and symptom relief (Symbicort Single Inhaler Therapy*) – compared with a higher maintenance dose of budesonide in patients with moderate to severe asthma.

*Methods:* This was a 12-month, randomised, double-blind, parallel-group study. Symptomatic patients with asthma ($n = 1890$; mean age 43 years [range 11 years–80 years], mean baseline forced expiratory volume in 1 s [$FEV_1$] 70% of predicted, mean inhaled corticosteroid [ICS] dose 746 μg/day) received either budesonide (160 μg, 2 inhalations twice daily) plus terbutaline 0.4 mg as needed or a daily maintenance dose of budesonide/formoterol (160/4.5 μg, 2 inhalations once daily) with additional inhalations of budesonide/formoterol 160/4.5 μg as needed. Time to first severe exacerbation (hospitalisation/emergency room [ER] treatment or systemic steroids due to asthma worsening or a fall in morning peak expiratory flow [PEF] to ≤ 70% of baseline on 2 consecutive days) was the primary outcome variable.

*Results:* A total of 1890 patients were randomised, of whom 1563 (83%) had severe

* Symbicort Single Inhaler Therapy is a trademark owned by the AstraZeneca group

asthma. The time to first severe exacerbation was prolonged by budesonide/formoterol single inhaler therapy ($p < 0.001$) compared with a higher dose of budesonide. The risk of having a severe exacerbation was 39% lower with budesonide/formoterol single inhaler therapy compared with budesonide ($p < 0.001$). The number needed to treat to prevent one severe exacerbation per year with budesonide/formoterol compared with budesonide was 5. The budesonide/formoterol group had 45% fewer severe exacerbations requiring medical intervention per patient compared with the budesonide group ($p < 0.001$). Budesonide/formoterol patients had fewer hospitalisations/ER treatments (15 vs 25 events, respectively [descriptive statistics]) and fewer treatment days with systemic steroids (1776 days vs 3177 days, respectively [descriptive statistics]) compared with budesonide patients. Budesonide/formoterol single inhaler therapy patients used less as-needed medication compared with budesonide patients (0.90 vs 1.42 inhalations/day; $p < 0.001$). The mean daily ICS dose was lower in the budesonide/formoterol group than in the budesonide group (466 μg/day vs 640 μg/day). Over the 12-month study period, the budesonide/formoterol group achieved asthma control sufficient to not require any additional as-needed medication on 60% of days. Overall, budesonide/formoterol single inhaler therapy gave 31 more asthma control days (a night and day with no asthma symptoms and no as-needed medication use) per patient-year and 12 additional undisturbed nights per patient-year compared with a higher dose of budesonide. Both treatments were well tolerated.

*Conclusion:* Budesonide/formoterol single inhaler therapy has the potential to provide a complete asthma management approach with one inhaler, demonstrating a high level of efficacy in patients with moderate to severe asthma.

## Introduction

Despite the availability of international asthma guidelines and effective anti-inflammatory and bronchodilator medications, many patients continue to suffer from poorly controlled asthma[1]. This is partly due to poor adherence to inhaled corticosteroid (ICS) therapy, as patients often over-rely on their short-acting $\beta_2$-agonist reliever medication in order to achieve rapid relief from symptoms, at the expense of their daily maintenance therapy. Consequently, the underlying inflammation associated with asthma may be undertreated, allowing symptoms to escalate further and increasing the risk of exacerbations. Evidence suggests that the use of multiple inhalers for daily maintenance therapy and reliever medication also contributes to poor adherence to asthma treatment[2].

The introduction of single inhalers combining an ICS with a long-acting $\beta_2$-agonist represents a key development in asthma management. There are currently two products available: budesonide/formoterol (Symbicort Turbuhaler*) and salmeterol/fluticasone (Seretide Diskus†). Both budesonide/formoterol and salmeterol/fluticasone are usually administered via fixed dosing regimens, whereby patients receive a fixed daily maintenance dose of medication and have a separate inhaler containing reliever medication for as-needed relief from symptoms. An alternative treatment strategy, developed for budesonide/formoterol, involves patients adjusting the maintenance dose in response to their current level of asthma control (referred to as adjustable maintenance dosing) – increasing the dose during periods of worsening asthma and reducing it when control is achieved. This ensures that the minimum effective dose of ICS is used to maintain control in line with guideline recommendations[3].

Studies comparing both fixed and adjustable maintenance dosing regimens with budesonide/formoterol demonstrated that adjustable maintenance dosing provides superior efficacy with a lower overall steroid load compared with traditional asthmatherapy[4,5]. Budesonide/formoterol adjustable maintenance dosing has also been compared with fixed-dose salmeterol/fluticasone in patients with moderate to severe asthma[6]. In this study, patients received either fixed dosing with budesonide/formoterol or salmeterol/fluticasone or adjustable maintenance dosing with budesonide/formoterol[6], with all patients using a short-acting $\beta_2$-agonist as reliever medication. Patients in the adjustable maintenance dosing group received a written self-management plan stipulating the course of action to take in the event of asthma worsening. Adjustable maintenance dosing with budesonide/formoterol provided more effective asthma control, reducing the rate of severe exacerbations by 40% compared with fixed-dose salmeterol/fluticasone ($p = 0.018$)[6]. Budesonide/formoterol adjustable maintenance dosing and fixed dosing treatment were equally well tolerated[4–6].

Evidence suggests, however, that written action plans are not widely used in practice[7,8]. In addition, action plans often advise patients to step up treatment after

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† Seretide and Diskus are trademarks of the GlaxoSmithKline group

2 days of awakenings, increased reliever use or falls in peak expiratory flow (PEF), thus introducing a time lag between an asthma worsening and increasing medication, which could reduce the effectiveness of this approach. Furthermore, action plans can involve different treatment regimens with multiple inhalers, which may introduce an element of complexity and impact on patient adherence[9].

We hypothesised that using a novel asthma treatment strategy with a combination inhaler for both maintenance and relief in patients with moderate to severe asthma would provide more effective asthma control compared with a traditional fixed dosing regimen. With this strategy – budesonide/formoterol single inhaler therapy – patients receive a low daily dose of budesonide/formoterol for maintenance therapy and take additional doses as needed for symptom relief. Importantly, patients do not need a separate inhaler for reliever medication with budesonide/formoterol single inhaler therapy because formoterol has an onset of action as fast as salbutamol, 1–3 min after inhalation[10,11]. Indeed, studies have shown that formoterol[12,13] and budesonide/formoterol[14] are as effective as salbutamol in providing relief from severe acute bronchospasm in patients presenting to an emergency room (ER). Furthermore, the efficacy and tolerability of as-needed formoterol have been demonstrated in a large randomised study involving 18 000 patients[15]. In this study, formoterol as needed reduced exacerbations when used in addition to maintenance therapy with either ICS or ICS plus a long-acting $\beta_2$-agonist[15].

As budesonide/formoterol single inhaler therapy delivers both maintenance therapy and as-needed medication, it has the potential to provide a complete management strategy with one inhaler, therefore simplifying asthma therapy. A key advantage of budesonide/formoterol single inhaler therapy compared with both fixed and adjustable dosing regimens is that patients can easily adjust their medication immediately, at the onset of symptoms, by taking additional inhalations as needed. Consequently, budesonide/formoterol single inhaler therapy can provide timely increases in both anti-inflammatory and bronchodilator medications, thereby preventing undertreatment and reducing the risk of exacerbations and periods with poor symptom control.

The efficacy of budesonide/formoterol single inhaler therapy has been demonstrated previously in a 6-month study in patients with mild to moderate asthma[16]. In the current study, we compared the efficacy and safety of budesonide/formoterol single inhaler therapy (160/4.5 µg 2 inhalations once daily plus additional doses as needed) with a higher maintenance dose of budesonide alone (160 µg 2 inhalations twice daily) plus terbutaline as needed in patients with moderate to severe asthma, over 12 months.

## Patients and methods

This randomised, double-blind, double-dummy, active-controlled study with a parallel-group design was conducted in 211 centres in the following countries: Argentina, Australia, Canada, Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, Mexico, The Netherlands, New Zealand, Norway, Portugal, Russia, South Africa and Turkey. The first patient was enrolled on 23 May 2001, with the last patient completing the study on 22 January 2003. All patients were outpatients recruited from hospital or primary care settings. The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and local regulations, each study centre having received ethical approval of the protocol prior to study commencement. All patients and parents/guardians of patients aged < 18 years were required to give written informed consent before any study-related procedures were performed.

### Study Design

Male and female patients aged 12 years–80 years with a diagnosis of asthma (as defined by the American Thoracic Society[17]) for at least 6 months were eligible for inclusion in the study if they had: (i) a history of ≥ 1 clinically important asthma exacerbations as judged by the investigator 1 month–12 months prior to study entry (Visit 1); (ii) used ICS (any brand) at a dose of 400 µg/day–1600 µg/day for at least 3 months and at a constant dose for at least 30 days prior to study entry; (iii) a forced expiratory volume in 1 s ($FEV_1$) 50%–90% of predicted normal; (iv) ≥ 12% reversibility in increase from baseline $FEV_1$ 15 min after inhalation of terbutaline sulphate 1 mg (Bricanyl Turbuhaler; AstraZeneca, Sweden). Additionally, for patients aged ≥ 18 years, an increase in baseline $FEV_1$ of ≥ 200 mL within 15 min of inhalation of terbutaline was required at study entry. Patients were excluded from the study if they had received systemic steroids or inhaled cromones within 30 days of study entry; if they had taken ≥ 3 courses of systemic steroids in the last 6 months; if they had cardiovascular disease or other significant disorders; if they had experienced a respiratory tract infection affecting asthma in the last 30 days; or if they were smokers with a smoking history of > 10 pack-years.

Patients completed a 2-week run-in period to collect baseline data, during which they continued to use their regular dose of ICS and took inhalations of terbutaline 0.5 mg (metered dose corresponding to a delivered dose of 0.4 mg) (Bricanyl; AstraZeneca, Sweden) as needed administered via a Turbuhaler. Patients were only eligible for randomisation if they were symptomatic and had moderate to severe asthma based on their level of

treatment and a history of clinically important exacerbations. Patients were not eligible if they had taken more than 10 inhalations of as-needed medication on any day during run-in.

All eligible patients were randomised to 12 months' treatment with either budesonide/formoterol single inhaler therapy 160/4.5 μg (Symbicort; AstraZeneca, Sweden) 2 inhalations once daily in the evening with additional inhalations as needed, or budesonide 160 μg (Pulmicort; AstraZeneca, Sweden) 2 inhalations twice daily in the morning and evening plus terbutaline 0.4 mg as needed. All study drugs were administered via Turbuhaler as delivered doses (a delivered dose of 160 μg budesonide corresponds to a metered dose of 200 μg and a delivered dose of 4.5 μg formoterol corresponds to a metered dose of 6 μg). Patients were not instructed to rinse their mouth with water following inhalation of the study drugs. Patients were allowed to take a maximum of 10 as-needed inhalations of either budesonide/formoterol or terbutaline per day. If > 10 inhalations were required in a single day, patients were asked to contact the investigator for reassessment.

### *Exacerbation Treatment*

All severe exacerbations were to be treated with a 10-day course of oral prednisolone 30 mg/day. If the patient needed > 10 days of treatment with prednisolone, the 11th day of treatment was considered to be the start of a second severe exacerbation. A deterioration of asthma resulting in the need for 3 courses of systemic steroids during 3 months, or a total of 5 courses during the study, led to the patient being withdrawn.

### *Blinding and Randomisation*

To ensure treatment blinding, a double-dummy design was employed so that each patient received three identical Turbuhalers (labelled as inhaler 1, 2 or 3). Patients were instructed to take 2 inhalations from inhaler No. 1 (containing budesonide or placebo for patients in the single inhaler therapy group) every morning upon rising and 2 inhalations of inhaler No. 2 (containing budesonide or budesonide/formoterol) every evening before going to bed. Inhaler No. 3 (containing treatment-specific reliever medication – budesonide/formoterol or terbutaline) could be used as needed when patients experienced asthma symptoms.

The randomisation code was prepared at the sponsor's site by a person not involved in the analysis of data. Computerised randomisation of treatment was performed using the computer program RandLink. Patients were randomised in balanced blocks sequentially according to their enrolment code. Treatment codes were not broken until all decisions on the availability of patient data had been made, except in the case of medical emergencies.

## Efficacy Evaluations

The primary outcome variable was time to first severe exacerbation. A severe exacerbation was defined as asthma worsening resulting in hospitalisation or ER treatment, the need for systemic steroids, or a fall in morning PEF to ≤ 70% of baseline on 2 consecutive days. Severe exacerbations that required medical intervention (hospitalisation/ER treatment or systemic steroids) were also analysed. A mild exacerbation day was defined as asthma worsening resulting in either: night-time awakening(s), a ≥ 20% decrease in morning PEF from baseline or an increase of ≥ 2 inhalations of reliever medication over a 24-h period compared with baseline. A mild exacerbation was defined as two consecutive mild exacerbation days of the same type (listed above).

PEF measurements were performed by the patient using a Mini-Wright peak flow meter (Clement Clark, Harlow, UK), following careful instruction, and were recorded on diary cards. Spirometric measurements were performed at all clinic visits within ± 1 h of the time of the first reading at baseline (randomisation; Visit 2), usually between 07:00 and 10:00, and in accordance with the European Respiratory Society recommendations[18].

Daytime and night-time asthma symptoms were recorded by patients on diary cards, graded on a scale of 0–3 (0 = no symptoms; 1 = aware of asthma symptoms but can easily tolerate them; 2 = asthma causing enough discomfort to cause problems with normal activities/sleep; 3 = unable to do normal activities/sleep because of asthma). These scores were summed to calculate the total daily asthma symptom score (scale of 0–6). Patients also recorded night-time awakenings due to asthma symptoms. Each morning and evening, patients recorded the number of inhalations of maintenance and as-needed medication taken. The percentage of symptom-free days (defined as a night and a day with no asthma symptoms and no night-time awakenings due to asthma) and the percentage of reliever medication-free days (defined as a day and a night with no reliever medication use) were calculated from diary card data, to provide an overall measure of symptom control. These endpoints were combined to determine the percentage of asthma-control days (defined as a night and a day with no asthma symptoms and no intake of reliever medication, and a night with no awakenings due to asthma symptoms).

## Clinical Safety Assessments

The incidence and intensity of adverse events were recorded at all clinic visits during the treatment period. Adverse events and serious adverse events were reported spontaneously or observed and recorded in

response to a standard question asked by the investigator: 'Have you had any health-related problems since the previous visit?'

Routine laboratory assessments and morning plasma (p)-cortisol analysis were performed in a subgroup of patients at baseline and after 6 months and 12 months of treatment. An adrenocorticotropic hormone (ACTH) stimulation test was also performed to assess adrenal function at baseline and after 12 months of treatment. p-cortisol concentrations were analysed using a gas chromatography and mass spectrometry method with the lower limit of quantification at 20 nmol/L, as described by Hsu *et al.*[19]. Vital signs and electrocardiogram measurements were also assessed.

### Statistical Analysis

All efficacy analyses were performed using intent to treat analysis on all randomised patients with data available after randomisation. All hypothesis testing was done using two-sided alternative hypotheses and $p$-values < 5% were considered statistically significant. Time to first severe exacerbation – the primary outcome variable – was compared between treatment groups using a log-rank test and a Cox proportional hazards model was used to compare treatments and calculate instantaneous risk. Assuming the true incidence of severe asthma exacerbations was 25% in one treatment group, in order to have an 80% probability of detecting a 19.2% reduction in incidence of severe exacerbations in the other treatment group (at the two-sided 5% level) a sample size of $n = 800$ per group was required. Time to first severe exacerbation requiring medical intervention and time to first mild exacerbation were also analysed as described above.

The total number of severe exacerbations requiring medical intervention (i.e. excluding PEF falls not recorded as severe exacerbations) and mild exacerbation days were compared between groups using a Poisson regression model. Confidence intervals (CIs) and $p$-values were adjusted for overdispersion. For all patient diary card variables and the percentage of mild exacerbation days, analysis was performed in terms of change from baseline. Baseline was defined as the average over the last 10 days of run-in and treatment as the average of all available data over the entire treatment period (excluding data from the day of randomisation). For $FEV_1$, baseline was the value measured at randomisation (Visit 2) and treatment was the mean of the available data from Visits 3–7. Changes from baseline were analysed by analysis of variance (ANOVA), with treatment and country as fixed factors and the baseline value as a covariate. The adjusted mean change from run-in was obtained from the analysis model and treatment differences and 95% CIs were calculated.

The change in morning p-cortisol from baseline (Visit 2) to end of treatment (Visit 7) was compared between treatment groups using a multiplicative (log transformation of data) ANOVA. For ACTH-stimulated p-cortisol, both the maximal p-cortisol after stimulation and the increase in p-cortisol from pre- to post-test were compared between treatments. A multiplicative ANOVA model was used to assess the change in maximal p-cortisol after ACTH stimulation; an additive ANOVA was performed to assess any increase in p-cortisol from before to after the test.

## Results

From a total of 2089 patients enrolled in the study, 1890 patients were randomised to treatment with either budesonide/formoterol single inhaler therapy ($n = 947$) or a higher maintenance dose of budesonide alone ($n = 943$) (Figure 1). All randomised patients were included in the 12-month efficacy and safety analysis ($n = 1890$). During the study, 397 protocol deviations were reported involving a total of 306 patients. The most common protocol deviation was randomisation in error, with a total of 80 patients (4%) reported to have at least one deviation of this nature (43 patients in the budesonide/formoterol group and 37 patients in the budesonide group). No protocol violation occurring during the study justified the exclusion of patients' data from the analysis.

Baseline characteristics were comparable between the treatment groups (Table 1). At baseline, 45% of patients in the budesonide/formoterol group and 44% of patients in the budesonide group were already using ICS plus a long-acting $\beta_2$-agonist or ICS/long-acting $\beta_2$-agonist combinations (Table 1). Of the 1890 patients randomised, the majority (1563 patients [83%]) were classified as having severe asthma according to modified Global Initiative for Asthma (GINA) guidelines[3]. Self-reported adherence to study medication was high (99%) and similar for both treatment groups.

### Severe Exacerbations

The time to first severe exacerbation was significantly prolonged by treatment with budesonide/formoterol single inhaler therapy compared with a higher dose of budesonide ($p < 0.001$). The instantaneous risk of having a severe exacerbation was 39% lower for patients receiving budesonide/formoterol than for those treated with budesonide ($p < 0.001$) and fewer patients in this group experienced a severe exacerbation compared with the budesonide group (170 vs 259 patients, respectively) (Table 2). The reductions in all types of severe exacerbations are shown in Figure 2.

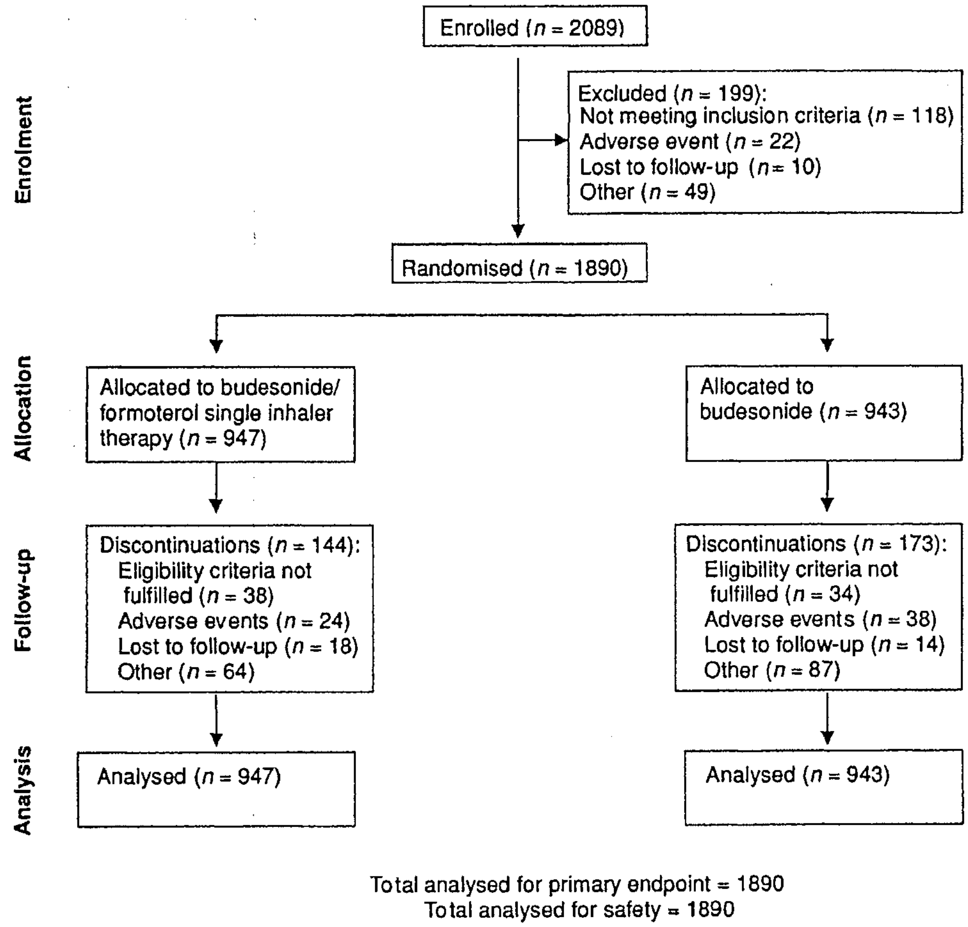



*Figure 1. Patient flow during the study. Patients received either budesonide/formoterol single inhaler therapy (budesonide/formoterol 160/4.5 μg 2 inhalations once daily plus additional inhalations as needed) or budesonide 160 μg 2 inhalations twice daily plus terbutaline 0.4 mg as needed for 12 months*

*Table 1. Baseline clinical characteristics of patients*

| Characteristic* | BUD/FORM ($n$ = 947) | BUD + SABA ($n$ = 943) |
|---|---|---|
| Male/female | 393/554 | 405/538 |
| Age, years (range) | 43 (12–79) | 43 (11–80) |
| Asthma duration, years (range) | 12 (1–65) | 12 (1–71) |
| $FEV_1$, % predicted normal (range)† | 70 (46–102) | 70 (37–95) |
| $FEV_1$, % reversibility† | 24 (7–152) | 24 (7–171) |
| ICS dose at entry, μg (range)† | 744‡ (250–2000) | 748‡ (400–2000) |
| Asthma medication at study entry, $n$ (%) | | |
| inhaled long-acting $\beta_2$-agonists | 328 (35) | 328 (35) |
| combination of inhaled long-acting $\beta_2$-agonists and ICS | 95 (10) | 83 (9) |
| Reliever use, number of inhalations/day (range) | 1.9 (0.0–15.6) | 2.0 (0.0–9.2) |
| Asthma symptom score, scale 0–6 (range) | 1.8 (0.0–6.0) | 1.9 (0.0–6.0) |
| Symptom-free days, % (range) | 10 (0–100) | 10 (0–100) |
| Asthma-control days, % (range) | 8 (0–100) | 8 (0–90) |

*All values are presented as absolute numbers or as mean (range), except asthma duration (median)

†Range indicates some patients in the intention to treat population had minor deviations in inclusion criteria that did not result in exclusion

‡Expressed as metered dose. A metered dose of 744 μg is equivalent to a delivered dose of 595 μg and a metered dose of 748 μg is equivalent to a delivered dose of 598 μg

BUD = budesonide; $FEV_1$ = forced expiratory volume in 1 s; FORM = formoterol; ICS = inhaled corticosteroid; SABA = short-acting $\beta_2$-agonist

*Table 2. Primary outcome analysis of patients*

| Exacerbation | Number (%) of patients with event | | Instantaneous risk of first exacerbation (hazard ratio; 95% CI) |
|---|---|---|---|
| | BUD/FORM ($n$ = 947) | BUD + SABA ($n$ = 943) | |
| All severe exacerbations | 170 (18) | 259 (27) | 0.61 (0.50, 0.74)* |
| Severe exacerbations requiring medical intervention | 137 (14) | 212 (22) | 0.61 (0.49, 0.75)* |

*Between-group difference: $p < 0.001$
BUD = budesonide; CI = confidence interval; FORM = formoterol; SABA = short-acting $\beta_2$-agonist

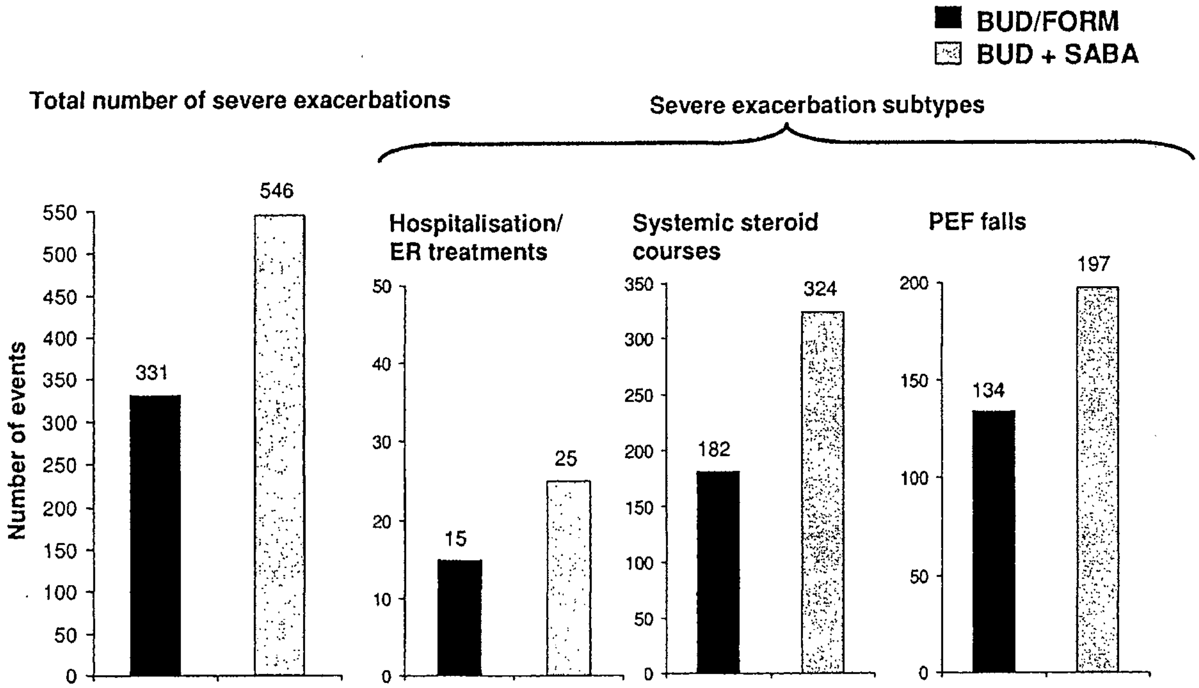



*Figure 2. Severe exacerbations by type. A severe exacerbation was defined as asthma worsening resulting in hospitalisation/emergency room (ER) treatment; treatment with systemic steroids or a fall in morning peak expiratory flow (PEF) to ≤ 70% of baseline on 2 consecutive days. The total number of severe exacerbations is the sum of all exacerbations due to PEF falls, systemic steroid courses and hospitalisation/ER treatments. Patients received either budesonide/formoterol single inhaler therapy (budesonide/formoterol 160/4.5 μg 2 inhalations once daily plus additional inhalations as needed) or budesonide 160 μg 2 inhalations twice daily plus terbutaline 0.4 mg as needed for 12 months. BUD, budesonide; FORM, formoterol; SABA, short-acting $\beta_2$-agonist*

Budesonide/formoterol single inhaler therapy resulted in fewer hospitalisations/ER treatments during the study compared with the budesonide group (15 vs 25 events, respectively [descriptive statistics]) (Figure 2). Patients receiving budesonide/formoterol single inhaler therapy required 142 fewer courses of systemic steroids compared with those receiving budesonide (182 vs 324 courses, respectively [descriptive statistics]) (Figure 2). A high proportion of exacerbations were defined by the PEF fall criterion in patient diaries (331 events) but were not recorded as severe exacerbations by the investigator: only 30 such events (9%) recorded in patient diaries were included in the case report forms by the investigator as confirmed exacerbations requiring treatment. When these untreated exacerbations were excluded from the analysis, budesonide/formoterol single inhaler therapy still increased the time to first severe exacerbation requiring medical intervention compared with budesonide (with an identical reduction in instantaneous risk [39%; $p < 0.001$]) (Table 2). The rate of severe exacerbations requiring medical intervention/patient was reduced by 45% with budesonide/formoterol single inhaler therapy compared

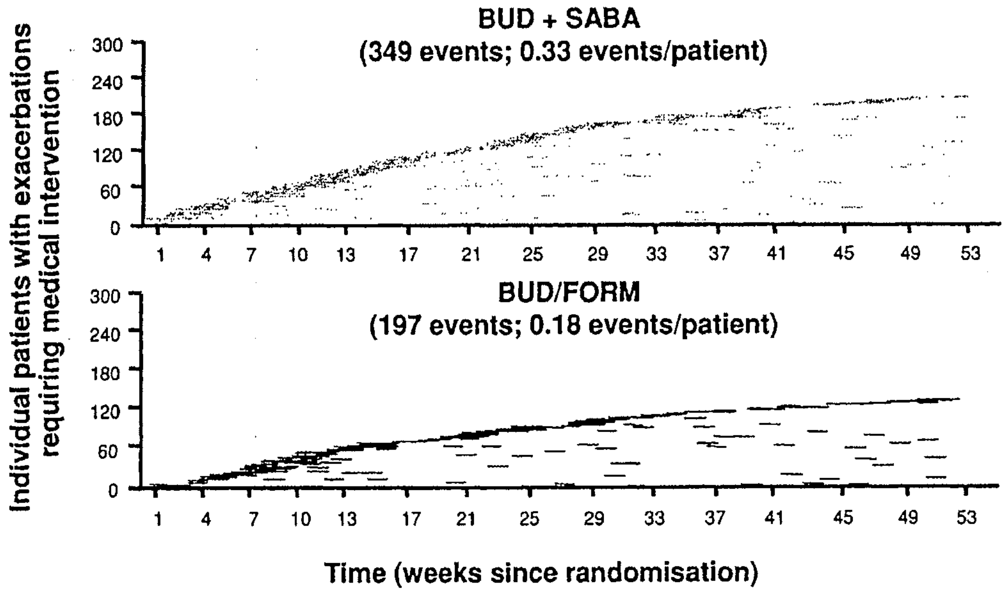



*Figure 3. Total number of severe exacerbations requiring medical intervention over time for individual patients during the 12-month treatment period. The x-axis represents time and each number on the y-axis represents an individual patient. Each single line (—) represents one exacerbation for an individual patient. Exacerbations > 10 days in duration were considered as multiple events. Individual patients with > 1 exacerbation are shown as broken or extended lines in the same horizontal position. Patients received treatment with budesonide/formoterol single inhaler therapy (budesonide/formoterol 160/4.5 μg 2 inhalations once daily plus additional inhalations as needed) or budesonide 160 μg 2 inhalations twice daily plus terbutaline 0.4 mg as needed. The rate of severe exacerbations requiring medical intervention/patient was reduced by 45% with budesonide/formoterol single inhaler therapy vs budesonide (95% confidence intervals [CI]: 34%–54%; p < 0.001). BUD, budesonide; FORM, formoterol; SABA, short-acting $\beta_2$-agonist*

with budesonide (95% CI: 34%–54%; $p < 0.001$). The total number of individual severe exacerbations requiring medical intervention over 12 months was reduced by 152 with budesonide/formoterol single inhaler therapy (first and repeated events totalled 197 events in the budesonide/formoterol group vs 349 events in the budesonide group) (Figure 3).

The number needed to treat (NNT) to avoid 1 exacerbation over 1 year with budesonide/formoterol single inhaler therapy vs budesonide was 5. Therefore, for every 100 patients treated with budesonide/formoterol single inhaler therapy for 1 year, there would be 20 fewer severe exacerbations requiring medical intervention compared with budesonide.

The severity of the exacerbations was further explored using mean profiles of diary card variables during severe exacerbations. Specifically, daily symptom scores, as-needed medication use/day and daily morning PEF were assessed for the period from 14 days before until 14 days after the start of each severe exacerbation. These profiles revealed generally lower symptom levels, lower as-needed medication use and higher PEF values for patients receiving budesonide/formoterol single inhaler therapy compared with those receiving budesonide.

## Mild Exacerbations

Patients in the budesonide/formoterol group had a significantly longer time to first mild exacerbation compared with the budesonide group ($p < 0.001$). The instantaneous risk of experiencing a mild exacerbation was 32% lower with budesonide/formoterol treatment compared with fixed dosing with budesonide (95% CI: 25%–39%; $p < 0.001$). Budesonide/formoterol reduced the percentage of mild exacerbation days by 6.5% compared with budesonide (95% CI: –8.54, –4.39; $p < 0.001$).

## Symptoms and Reliever Medication Use

Patients receiving budesonide/formoterol for both maintenance and symptom relief had significantly lower daytime and night-time asthma symptom scores compared with those receiving budesonide and as-needed terbutaline (Table 3), resulting in a lower total symptom score (Figure 4a). The percentage of nights with awakenings was significantly reduced with budesonide/formoterol ($p < 0.001$; Table 3), resulting in 12 fewer nights with awakenings/patient-year compared with budesonide. In addition, patients in the

*Table 3.* Mean patient diary card variables

| Efficacy variable | BUD/FORM ($n$ = 947) | | BUD + SABA ($n$ = 943) | | | |
|---|---|---|---|---|---|---|
| | Baseline* mean (range) | Treatment mean (range) | Baseline* mean (range) | Treatment mean (range) | Between-group difference† (95% CI) | $p$-value |
| Morning PEF, L/min | 339.2 (77–670) | 372.1 (100–751) | 335.8 (104–749) | 348.5 (93–805) | 20.3 (16.5, 24.1) | < 0.001 |
| Evening PEF, L/min | 349.0 (77–722) | 369.6 (99–720) | 348.1 (101–718) | 354.7 (91–808) | 14.0 (10.4, 17.5) | < 0.001 |
| Daytime asthma symptom score (0–3) | 1.09 (0.0–3.0) | 0.66 (0.0–3.0) | 1.11 (0.0–3.0) | 0.77 (0.0–3.0) | –0.10 (–0.14, –0.06) | < 0.001 |
| Night-time asthma symptom score (0–3) | 0.75 (0.0–3.0) | 0.42 (0.0–3.0) | 0.79 (0.0–3.0) | 0.55 (0.0–3.0) | –0.11 (–0.15, –0.07) | < 0.001 |
| Total asthma symptom score (0–6)‡ | 1.84 (0.0–6.0) | 1.08 (0.0–6.0) | 1.90 (0.0–6.0) | 1.32 (0.0–6.0) | –0.21 (–0.28, –0.13) | < 0.001 |
| Night-time awakenings (%) | 22.6 (0–100) | 9.4 (0–100) | 23.5 (0–100) | 13.0 (0–100) | –3.3 (–4.8, –1.7) | < 0.001 |
| Symptom-free days (%)§ | 9.8 (0–100) | 41.7 (0–100) | 9.7 (0–100) | 34.0 (0–100) | 7.5 (4.5, 10.4) | < 0.001 |
| As-needed free days (%)¶ | 29.3 (0–100) | 59.8 (0–100) | 26.3 (0–100) | 47.2 (0–100) | 11 (8.2, 13.8) | < 0.001 |
| Asthma-control days (%)** | 7.9 (0–100) | 38.3 (0–100) | 7.5 (0–90) | 29.3 (0–100) | 8.6 (5.7, 11.4) | < 0.001 |

*Mean of last 10 days of run-in
†From ANOVA model
‡Sum of the mean daytime and night-time scores
§A night and day with no symptoms and no asthma-related night-time awakenings
¶A night and day with no use of as-needed medication
**A night and day with no symptoms (night or day), no use of reliever medication and no asthma-related night-time awakenings
BUD = budesonide; CI = confidence interval; FORM = formoterol; PEF = peak expiratory flow; SABA = short-acting $\beta_2$-agonist

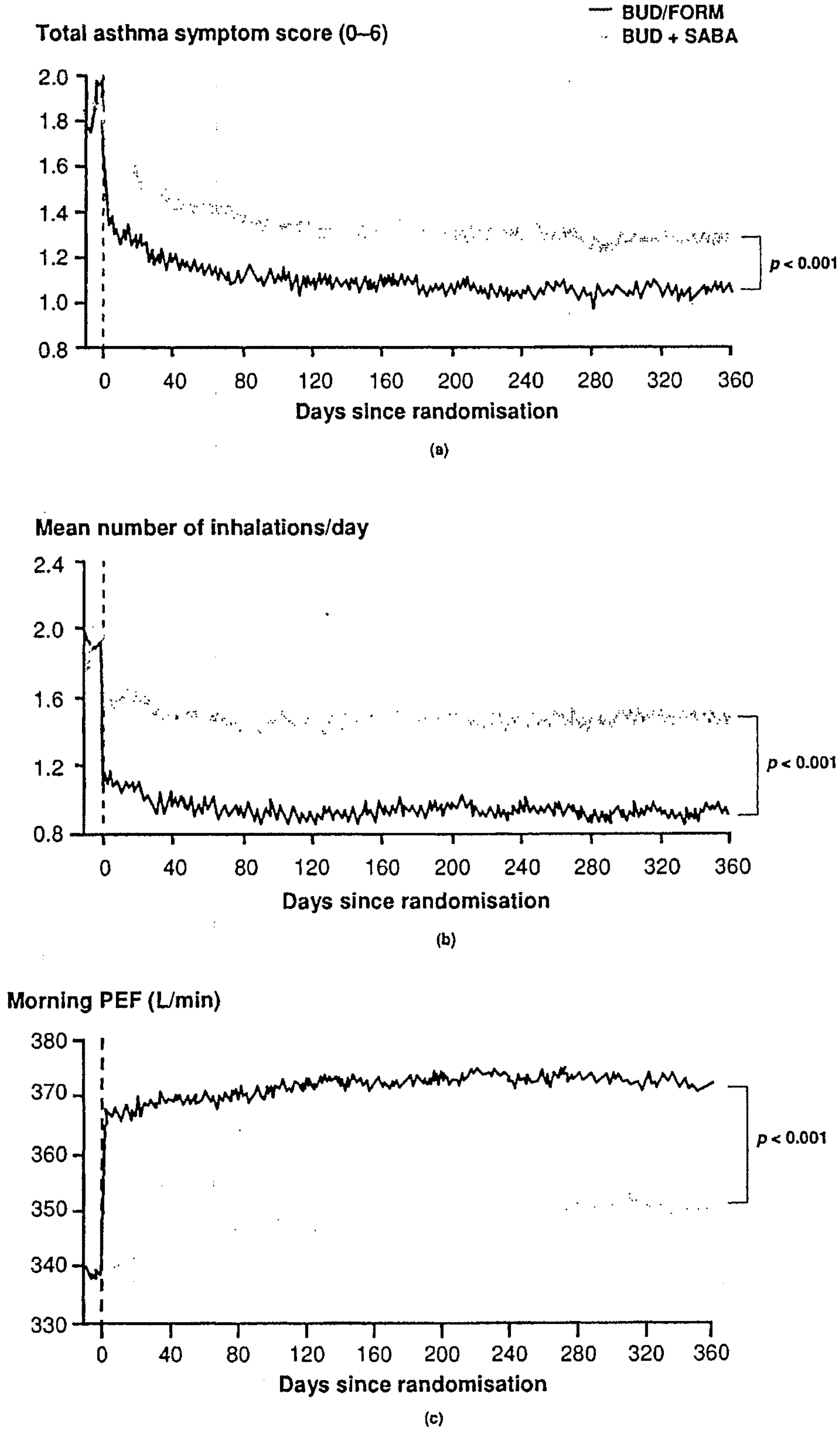
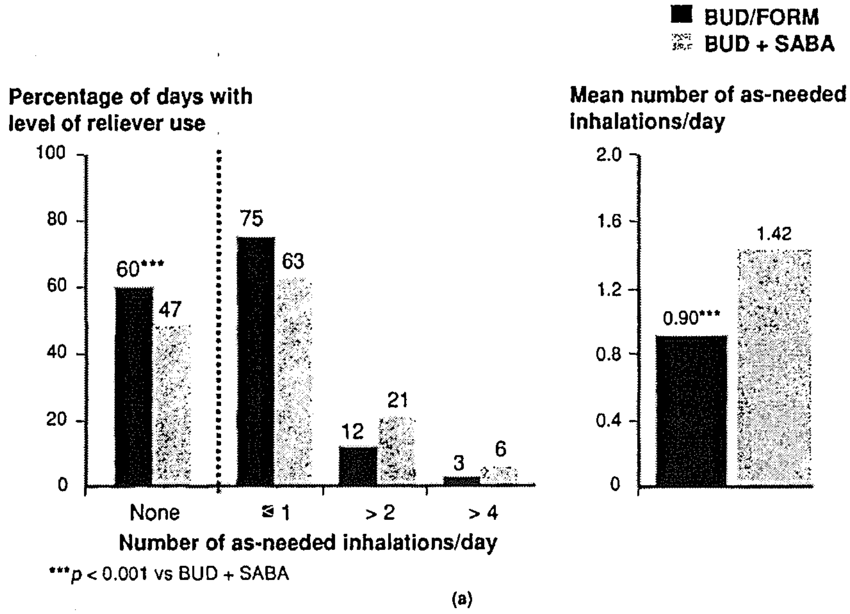



*Figure 4. Diary card data over 12 months' treatment with either budesonide/formoterol single inhaler therapy (budesonide/formoterol 160/4.5 μg 2 inhalations once daily plus additional inhalations as needed) or budesonide 160 μg 2 inhalations twice daily plus terbutaline 0.4 mg as needed. Analysis was performed on change from run-in over the whole treatment period. (a) Mean total asthma symptom score (i.e. sum of daytime and night-time scores) (each scale ranged from 0 = no symptoms to 3 = unable to do normal activities [or sleep] because of asthma); (b) mean daily as-needed medication use per 24 h and (c) mean morning peak expiratory flow (PEF). BUD, budesonide; FORM, formoterol; SABA, short-acting $\beta_2$-agonist*



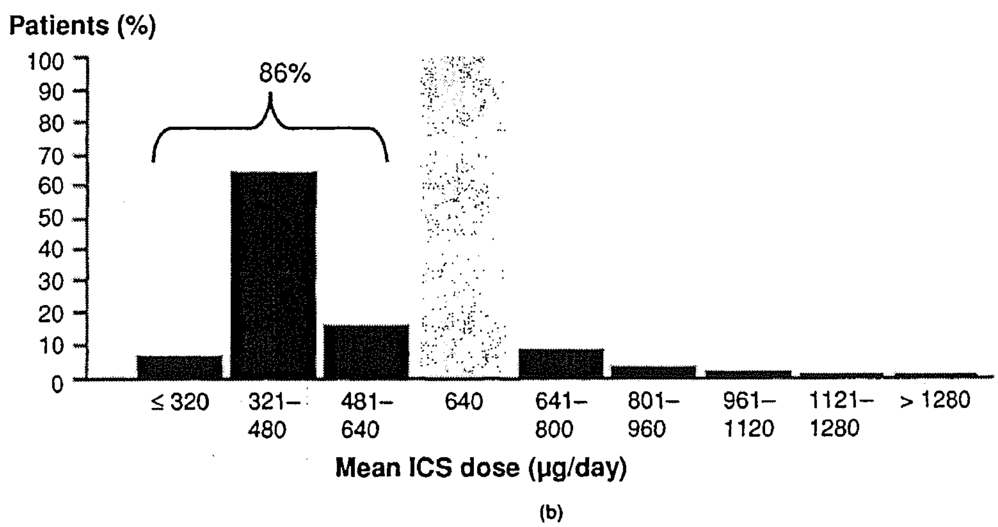




*Figure 5. (a) Proportion of days with different levels of as-needed medication use (left panel) and mean overall daily use (right panel) and (b) overall distribution of mean daily inhaled corticosteroid use in patients treated with either budesonide/formoterol single inhaler therapy (budesonide/formoterol 160/4.5 μg 2 inhalations once daily plus additional inhalations as needed) or budesonide 160 μg 2 inhalations twice daily plus terbutaline 0.4 mg as needed. BUD, budesonide; FORM, formoterol; ICS, inhaled corticosteroid; SABA, short-acting $\beta_2$-agonist*

budesonide/formoterol group had significantly more symptom-free days ($p < 0.001$; Table 3) – corresponding to an additional 27 days/patient-year – compared with the budesonide group. Treatment with budesonide/formoterol also resulted in significantly more asthma-control days ($p < 0.001$; Table 3), providing 31 more days/patient-year free from asthma symptoms, night-time awakenings and reliever medication use, compared with budesonide.

Patients in the budesonide/formoterol single inhaler therapy group used significantly less as-needed medication/day compared with the budesonide group during the treatment period (0.90 vs 1.42 inhalations/day, respectively; $p < 0.001$). As-needed medication use declined slightly during the initial months of the study in both treatment groups before stabilising (Figure 4b). Treatment with budesonide/formoterol single inhaler therapy resulted in significantly more reliever-free days compared with a higher maintenance dose of budesonide ($p < 0.001$; Table 3). Once-daily maintenance dosing with budesonide/formoterol, without additional as-needed inhalations, was achieved on 60% of days, while

*Table 4. Incidence of pharmacologically predictable adverse events [number (%)]*

| Adverse event | BUD/FORM ($n$ = 947) | BUD + SABA ($n$ = 943) |
|---|---|---|
| Palpitation, tremor or tachycardia* | 16 (2) | 13 (1) |
| Dysphonia† | 23 (2) | 17 (2) |
| Candidiasis† | 11 (1) | 13 (1) |

*Adverse events frequently related to treatment with $\beta_2$-agonists
†Adverse events frequently related to treatment with ICS
BUD = budesonide; FORM = formoterol; ICS = inhaled corticosteroids; SABA = short-acting $\beta_2$-agonist

patients receiving budesonide twice daily did not use as-needed medication on 47% of days (between-group difference $p < 0.001$) (Figure 5a). The proportion of days during which patients used > 2 or > 4 as-needed inhalations in any one day was approximately twice as common with budesonide plus as-needed terbutaline (21% and 6% of days, respectively) compared with budesonide/formoterol single inhaler therapy (12% and 3% of days, respectively) (Figure 5a).

Overall, there was no evidence of overuse of reliever medication in the budesonide/formoterol single inhaler therapy group. Patients receiving budesonide/formoterol and budesonide plus as-needed terbutaline used > 10 inhalations of as-needed medication on 0.1% and 0.2% of days during the study, respectively, with only 22 patients in the budesonide/formoterol group using > 10 inhalations in any one day compared with 67 patients in the budesonide group.

## Total Steroid Dose

Patients using budesonide/formoterol for both maintenance and relief had a lower mean daily dose of ICS compared with those in the traditional fixed dosing group (466 µg/day vs 640 µg/day, respectively). The majority of patients in the budesonide/formoterol group (86%) had a mean daily ICS intake that was either equal to or lower than the maintenance dose of ICS used by patients in the budesonide group (640 µg) (Figure 5b). Additionally, patients in the budesonide/formoterol group needed 44% fewer treatment days with systemic steroids compared with the budesonide group (1776 vs 3177 treatment days, respectively [descriptive statistics]).

## Lung Function

Budesonide/formoterol single inhaler therapy resulted in a significantly greater increase in morning PEF compared with fixed dosing with budesonide (mean difference: 20.3 L/min; $p < 0.001$ [Table 3]). The large increase in morning PEF observed in patients treated with budesonide/formoterol was apparent from the start of treatment and was maintained throughout the 12-month treatment period (Figure 4c). Similarly, patients in the budesonide/formoterol group had significantly greater increases in evening PEF compared with those receiving budesonide (Table 3). Improvements in $FEV_1$ were significantly greater in patients receiving budesonide/formoterol single inhaler therapy compared with those receiving budesonide (treatment means were 2.54 L vs 2.45 L, respectively; mean difference: 0.10 L [95% CI: 0.071, 0.130; $p < 0.001$]).

## Safety

The incidence, frequency and profile of adverse events, and days of exposure to the investigational product were similar between treatment groups, with a total of 526/947 patients (56%) in the budesonide/formoterol group experiencing an adverse event compared with 533/943 patients (57%) in the budesonide group. Both treatments were well tolerated and adverse events were mainly mild to moderate in intensity. The most commonly reported adverse events in the budesonide/formoterol and budesonide groups were respiratory infection (172 [18%] vs 177 [19%] patients, respectively), bronchitis (63 [7%] vs 72 [8%] patients, respectively) and aggravated asthma (28 [3%] vs 43 [5%] patients, respectively). The incidence of adverse events related to ICS or $\beta_2$-agonists was low and similar between treatment groups (Table 4). A total of 113 serious adverse events were reported: 58 in the budesonide/formoterol single inhaler therapy group and 55 in the budesonide group. Two serious adverse events (atrial fibrillation and dizziness) – both in the budesonide/formoterol group – were considered by the investigator to be causally related to the investigational

product. Fewer patients in the budesonide/formoterol group discontinued the study as a result of adverse events (24 patients [3%] vs 38 patients [4%] in the budesonide group). Three deaths were reported during the study – one in the budesonide/formoterol group (peritoneal metastases) and two in the budesonide group (myocardial infarction and hypertrophic cardiomyopathy). None of these was judged to be causally related to the investigational products or directly related to asthma.

No clinically important differences were observed between treatment groups or over time during the 12-month treatment period for any of the laboratory variables studied. Mean morning p-cortisol concentrations remained stable over the study duration in both groups: 310 nmol/L at baseline and 306 nmol/L at the end of treatment with budesonide/formoterol vs 278 nmol/L at baseline and 254 nmol/L at the end of treatment with budesonide (mean ratio from baseline to end of treatment was 15% higher with budesonide/formoterol vs budesonide ($p = 0.06$). No statistically significant difference was observed between treatment groups for mean maximal p-cortisol concentration following ACTH stimulation, which increased during treatment in both groups: 598 nmol/L at baseline and 666 nmol/L at the end of treatment with budesonide/formoterol vs 621 nmol/L at baseline and 635 nmol/L at the end of treatment with budesonide (mean ratio from baseline to end of treatment was 8% higher with budesonide/formoterol compared with budesonide [$p = 0.40$]).

## Discussion

In this large-scale, double-blind, 12-month study involving over 1800 patients, we assessed whether a single inhaler containing budesonide/formoterol (Symbicort Turbuhaler) could be used safely and effectively for both maintenance therapy and symptom relief in patients with moderate to severe persistent asthma. Almost half the patients randomised were receiving ICS and a long-acting $\beta_2$-agonist at entry and most (83%) patients were classified as having severe asthma[3]. In this patient population, the budesonide/formoterol single inhaler therapy management approach was shown to be as well tolerated as a higher fixed dose of budesonide plus as-needed short-acting $\beta_2$-agonist, while providing superior asthma control – significantly reducing the risk of a severe exacerbation by 39% compared with a 2-fold higher dose of budesonide. Budesonide/formoterol single inhaler therapy also reduced nocturnal asthma symptoms, increased asthma-control days and improved lung function compared with a higher dose of budesonide.

The number of severe exacerbations with budesonide/formoterol single inhaler therapy was consistently lower throughout the 12-month study period (Figure 3). The reduction in the risk of severe exacerbations was larger than that observed in previous studies comparing budesonide plus formoterol with a 4-fold higher dose of budesonide in patients with moderate to severe asthma[20], or where salmeterol was added to fluticasone or beclomethasone and compared with a 2-fold higher dose of ICS alone[21]. In the meta-analysis reported by Shrewsbury and co-workers[21], although significantly fewer patients experienced moderate or severe exacerbations with the addition of salmeterol to ICS compared with those receiving a 2-fold higher dose of the ICS, the treatment difference (2.4% of patients) was not clinically important (NNT 41; $p = 0.03$)[21]. Conversely, in the current study the NNT to prevent 1 patient having a severe exacerbation requiring medical intervention per year with budesonide/formoterol vs a higher dose of budesonide alone was 5, suggesting that budesonide/formoterol single inhaler therapy can markedly improve exacerbation control.

Budesonide/formoterol single inhaler therapy improved daily asthma control, with 31 more asthma-control days/patient-year and 12 fewer nights with awakenings/patient-year than a higher dose of budesonide. The improved daily control was reflected by a sustained improvement in lung function and sustained reduction in as-needed medication use throughout the 12-month study compared with budesonide. The improved efficacy provided by this complete asthma management approach in a single inhaler was achieved with a mean budesonide intake of 466 μg/day compared with 640 μg/day in the budesonide group. Furthermore, systemic steroid treatment days were reduced with budesonide/formoterol single inhaler therapy compared with budesonide (1776 days vs 3177 days, respectively). Despite the majority of patients having severe asthma at study entry, budesonide/formoterol single inhaler therapy achieved optimal symptom control on 60% of days with a once-daily dosing regimen, without the need for additional as-needed inhalations.

The findings from this study in patients with moderate to severe asthma are in agreement with those from the study by Rabe *et al.*[16] in patients with mild to moderate asthma. The number of severe exacerbations resulting in hospitalisation was reduced by the ratio of 10:1 in favour of budesonide/formoterol plus additional inhalations as needed compared with a higher daily dose of budesonide[16]. Patients in this study used an average of 3 inhalations in total per day – 2 regular maintenance

inhalations plus 1.04 as-needed inhalations[16]. Other studies have also shown that adjusting the maintenance dose of budesonide/formoterol in response to symptoms as directed by a written action plan significantly reduced severe exacerbations compared with fixed dosing with either budesonide/formoterol[4,5] or salmeterol/fluticasone[6]. In contrast, a recent study in patients receiving > 700 μg/day ICS[22] has confirmed that delayed adjustments in ICS alone in response to a pre-defined fall in PEF at the peak of an exacerbation had little effect on preventing or ameliorating severe exacerbations. Thus, earlier and simultaneous adjustment of both monocomponents of the budesonide/formoterol combination may offer advantages in preventing exacerbations compared with adjusting the dose of ICS alone.

The budesonide/formoterol single inhaler therapy approach used in this study and by Rabe *et al.*[16] is differentiated from the adjustable maintenance dosing approach[4-6] because it achieves a more timely adjustment in both budesonide and formoterol therapy in relation to the onset of symptoms, without the need for patients to follow a complex written action plan. Using budesonide/formoterol in this way replaces as-needed short-acting bronchodilator therapy (used to treat routine symptoms) with a more effective treatment that provides immediate symptom relief and additional anti-inflammatory therapy, thus preventing symptoms from developing into exacerbations. Both anti-inflammatory and long-acting bronchodilator medications are delivered with every inhalation of budesonide/formoterol single inhaler therapy. This simplifies treatment because, unlike the adjustable maintenance dosing approach, there is no need for multiple inhalers or a complex action plan. Studies have shown that asthma symptoms and the subsequent use of a short-acting $\beta_2$-agonist for symptom relief increase at least 1 week before a full-blown exacerbation[23,24]. Thus, the increased dose and frequency of dosing with anti-inflammatory therapy in response to the first sign of asthma symptoms will coincide with the start of any potential exacerbation when using the budesonide/formoterol single inhaler therapy approach. Evidence suggests that increasing the dosing frequency of budesonide may be at least as important as increasing the total daily dose during periods of poor asthma control[25]. Findings from another study showed that an early increase in the dose and dosing frequency of budesonide in a 7-day burst, at the onset of asthma worsening, reduced the need for treatment with systemic steroids and was as effective as a regular 4-fold higher maintenance dose of budesonide over 6 months[26].

While this study confirms that budesonide/formoterol single inhaler therapy provides more effective asthma control compared with traditional asthma therapy with a higher dose of budesonide, we can only speculate on the mechanisms behind this. Only the single inhaler therapy group received formoterol. Consequently, the exact contribution of the regular maintenance dose of formoterol versus the contribution of the as-needed adjustments in the formoterol or budesonide dose in improving asthma control cannot be determined with the current study design. Previous studies, such as the FACET study[20], demonstrated that the use of maintenance formoterol improves daily asthma control compared with a 4-fold higher budesonide dose, while affecting the rate of severe exacerbations to a lesser extent than the higher dose of budesonide. Furthermore, the use of as-needed formoterol in patients receiving maintenance therapy with a high dose of budesonide has been reported to reduce severe exacerbations, although significant benefit was observed only when severe exacerbations defined by PEF falls were included in the analysis and while maintaining the budesonide dose at a high level in all groups[27]. It is reassuring that the present study showed that all types of exacerbations and all other aspects of asthma control were markedly improved in patients receiving budesonide/formoterol single inhaler therapy, including a 45% reduced rate of severe exacerbations requiring medical intervention, despite an overall reduction in regular budesonide therapy.

The potential of budesonide/formoterol to be used for both maintenance and relief of symptoms is unique to this combination inhaler because of the properties of the monocomponents. The onset of efficacy of budesonide/formoterol appears to be as rapid as salbutamol in both patients with stable asthma with methacholine-induced bronchoconstriction[28] and patients requiring medical attention with acute severe asthma[14]. The dose–response properties of budesonide[20,29] and formoterol[10,30] in improving asthma control and lung function mean that additional doses of budesonide/formoterol can be taken as needed to regain control of asthma. Budesonide/formoterol at occasional doses up to 1920/54 μg[31] and at regular doses of 1280/36 μg/day for 6 months[32] is well tolerated and effective, supporting the use of budesonide/formoterol as both maintenance and reliever medication.

In the present study, the incidence of adverse events related to ICS or $\beta_2$-agonist class effects was similar in both treatment groups, suggesting that budesonide/formoterol has a favourable tolerability profile when used for both maintenance and relief in patients with moderate to severe asthma. Moreover, despite the high proportion of patients with severe asthma in the current study, no significant overuse of as-needed medication occurred. Reassuringly, patients receiving budesonide/formoterol used on average only 2.9 inhalations per day – 2 regular daily inhalations plus 0.90 additional inhalations/day as needed[16]. Furthermore, while there was the potential to

receive increased doses of formoterol in the budesonide/formoterol single inhaler therapy group, there was little evidence of this. As-needed use exceeded 2 or 4 inhalations/day on twice as many days in the budesonide plus as-needed terbutaline group compared with the budesonide/formoterol single inhaler therapy group.

A remaining concern related to the use of long-acting $\beta_2$-agonists as a reliever is that – because they are so effective in reducing asthma symptoms – they may mask airway inflammation, causing an increase in the ICS dose in the lead-up to an attack to be delayed. This would result in undertreatment of airway inflammation, increasing the risk of severe or difficult-to-treat exacerbations. However, in a recent large study involving 18 000 patients where as-needed formoterol was compared with salbutamol as needed, formoterol was found to reduce severe exacerbations of all types, including hospitalisations[15]. An advantage of the budesonide/formoterol single inhaler therapy approach is that undertreatment with ICS is less of an issue because ICS is delivered with each as-needed inhalation, therefore treating the underlying inflammation. In the present study, exacerbations of all types were markedly reduced with budesonide/formoterol single inhaler therapy and the profiles of asthma symptoms, reliever-medication use and lung function during exacerbations were similar or improved compared with a higher dose of budesonide – possibly indicating that no masking of inflammation was evident in patients receiving budesonide/formoterol single inhaler therapy.

The prevention of severe exacerbations and improved exacerbation profile seen in the present study can be regarded as a good surrogate indicator of maintained inflammatory control with budesonide/formoterol single inhaler therapy. Further long-term studies are warranted, however, to confirm whether the overall improved efficacy achieved with this simplified treatment approach also extends to a similar reduction in relevant biomarkers of airway inflammation and remodelling compared with a higher fixed dose of ICS.

In conclusion, we have shown that a novel asthma management concept using budesonide/formoterol in a single inhaler for both maintenance therapy and relief from symptoms is a valid and beneficial strategy for the treatment of moderate to severe asthma – and could represent a potential advance in asthma treatment, both in terms of increased efficacy and a simplification of the treatment regimen.

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